

REMARKS

Claims 1-37 are pending. Claims 16-37 were withdrawn from consideration and claims 13-15 and 38-49 were previously cancelled. Claims 1, 4, 7, and 10 are amended. Support for the amendments can be found throughout the specification and claims as filed. Accordingly, no new matter has been added by way of amendment.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-12 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Tsien et al., (U.S. Patent No. 6, 469,154 (hereinafter “Tsien”)) in view of McWherter et al., 1999 (Biochemistry, vol. 38, pp. 4564-4571 (hereinafter “McWherter”)). Applicants respectfully disagree and traverse the rejection.

Nevertheless, without acquiescing to the basis of the rejection and solely to more fully and completely claim Applicants’ invention, Applicants have amended claims 1, 4, 7, and 10.

As amended claim 1 is directed to:

A method for assembling a modulatable fusion molecule polypeptide, comprising:
generating a circular permutation of an insertion nucleic acid sequence, wherein the insertion nucleic acid sequence encodes a polypeptide that recognizes an input signal; and

inserting the insertion sequence into an acceptor nucleic acid sequence, wherein the acceptor sequence encodes a polypeptide that produces an output signal provided the output signal is not fluorescence, wherein the fused insertion and acceptor sequences encode a modulatable fusion polypeptide having the **output signal functionally coupled to the input signal**.

Claims 4, 7, and 10 have been similarly amended.

The test of obviousness requires that one compare the claimed “subject matter as a whole” with the prior art “to which said subject matter pertains” 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, a suggestion or motivation to modify the reference or combine reference teachings must be present in the

references or in the general knowledge present in the art. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. The burden is on the Examiner to show that the references expressly or impliedly suggest all of the claim limitations. M.P.E.P. 2142. “There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons skilled in the art.” *In re Rouffet*, 149 F.3d 1350, 1357. In the absence of some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074.

Neither Tsien nor McWherter, either individually or in combination, teach or suggest the claimed method of making a **modulatable fusion polypeptide having the output signal functionally coupled to the input signal**.

Tsien describes fluorescent sensor polypeptides (Abstract). McWherter describes an IL-3R agonist domain fused to a cpG-CSF domain.

The molecules described in McWherter are not modulatable fusion proteins because the output signal of one ligand is **not** influenced by the input signal of the other ligand. The Examiner alleges that McWherter teaches a modulatable fusion protein in the paragraph bridging the left- and right-hand columns at page 4569. Applicants disagree. McWherter at the cited portion of page 4569 provides:

As discussed below, an additional and unexpected result was that the IL-3R agonist domain stabilized and/or enhanced the biological activity of the cpG-CSF domain when linked at certain breakpoints. Although the exact origin of this “restoration” effect is unknown, the addition of the hinge-IL-3R agonist residues may stabilize the cpG-CSF domain, either by the addition of stabilizing interactions or by removal of destabilizing interactions.

Contrary to the Examiner’s allegation, this section of McWherter does **not** describe a modulatable fusion protein where one part receives an **input signal** and the other part produces an **output signal**. Instead, it merely teaches a fusion protein of two agonists wherein the insertion of the first agonist stabilizes the structure of the second agonist. This stabilization is

not dependant on any input signal, it is merely a constitutive aspect of the structure of the fusion protein. Accordingly, the fusion protein described by McWherter is not a modulatable fusion protein.

CONCLUSION

For at least the foregoing reasons, each of the presently pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call Applicants' undersigned representative to discuss the application. Applicants thanks the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105. In view of the foregoing, Applicants request reconsideration and allowance of the pending claims.

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